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FUNCTIONAL IMAGING RESEARCH IN SCHIZOPHRENIA

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In the preceding decade, functional neuroimaging has emerged as a pivotal tool for psychiatric research. Techniques such as magnetic resonance imaging (MRI) and positron emission tomography (PET) help bridge the gap between genetic and molecular mechanisms and psychological and behavioral phenomena by characterizing brain dysfunction underlying psychiatric disorders on the neural systems level. This has been of particular relevance for schizophrenia research. This chapter reviews important fMRI studies in neurocognitive domains relevant for schizophrenia, such as motor, visual, auditory, attentional, and working memory function, as well as advances in the visualization of medication effects and the functional characterization of susceptibility genes.

The evolution of our understanding about the nature and treatment of disease is often linked to technological advances providing access to otherwise unobservable structures and processes. A case in point is the enormous benefit medicine as a whole has derived from the development and further improvement of imaging techniques (e.g., microscopy, sonography, computed tomography). Arguably, however, the discipline where imaging has had the largest impact on

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our understanding of the pathophysiology, but also the very concepts of the disease entities under study, is psychiatry. Psychiatry's challenge is unique in that it must provide a testable scientific account that spans levels of description leading from genes and elementary biological processes to disturbed behavior and social adaptation. Modern imaging techniques such as magnetic resonance imaging (MRI) and positron emission tomography (PET) provide access to a systems-level description of the relevant neurobiology that allows for relating the underlying cellular and genetic processes to the neurocognitive and psychopathological domain. This has contributed enormously to establish and anchor psychiatric research firmly in the broader neuroscience community. In consequence, our current understanding of psychiatric disorders is a neuroscientific one, characterized by the interpretation of disease states in the context of functional, biochemical, and microstructural alterations of the brain.

Without the insights provided by noninvasive medical imaging techniques, the progress made in psychiatric neuroscience in the past decade seems unthinkable. Even notions about the pathogenesis and treatment of psychiatric disorders that were regarded as polar opposites have begun to be understood in a unified framework of a neurobiologically founded diathesis-stress model. For example, the classical dichotomy of somatotherapy and psychotherapy is becoming obsolete as our understanding of functional brain alterations during these therapeutic modalities evolves and shows important commonalities (Goldapple *et al.*, 2004). Current evidence-based etiological models of schizophrenia point toward the key importance of interactions between predisposing vulnerability, mainly because of genetic susceptibility conferred by multiple risk genes, and environmental factors. The neurodevelopmental hypothesis proposes that schizophrenia emerges from intrauterine disturbances in temporolimbic–prefrontal interactions that manifest as clinical illness after adolescence (Weinberger, 1987). According to this hypothesis, the disturbed neural interaction leads to an impairment of prefrontal function manifesting as negative symptoms (e.g., blunted speech, lack of drive) and cognitive deficits, especially in the executive domain (e.g., working memory, selective attention). Because of deficient prefrontal control exerted on phylogenetically older brain areas, subcortical dopamine release in the basal ganglia is thought to become disinhibited, a phenomenon linked, possibly by the relevance of dopamine for the stabilization of cortical neural assemblies, to the emergence of positive symptoms like hallucinations and delusions (Meyer-Lindenberg *et al.*, 2002).

Since the early 1990s, physiological alterations of brain function have been investigated with functional magnetic resonance imaging (fMRI). In the beginning, the experimental procedures were rather simple, usually using a blockwise alternation of different stimulation conditions. In the following years, the methodological spectrum expanded to event-related task designs, which allow the analysis of brain responses to brief stimuli under conditions that

can rapidly change. Advances in the analysis of connectivity between brain regions allow for the characterization of dynamic network interactions. Further technical developments, including those in computational power and data storage, led to the development of scanners with ultra-fast gradient systems. Today, multichannel RF coils (array coils) can decrease acquisition time and/or increase signal-to-noise and spatial resolution substantially by simultaneous measurement of partial volumes. By using advanced acquisition schemes, whole brain data collection with highly resolved slices is now routinely done within a few seconds. In the past 4 years, the broad availability of clinical scanners has given rise to an enormous amount of fMRI studies in psychiatric research. Focussing on selected neurocognitive domains in schizophrenic patients, this chapter reviews important fMRI studies of the past decade. Because of the sheer volume of published results, our review cannot aim for all-inclusiveness and should best be read as a partial and necessarily subjective view of a vital and still expanding field.

I. Psychomotor Disturbances

Patients with schizophrenia frequently exhibit psychomotor disturbances. Manifestations range from involuntary motor acts, neurological soft signs (e.g., coordination deficits) to complex disorders of behavioral control and catatonic symptoms (Schroeder *et al.*, 1991; Vrtunski *et al.*, 1986). Although quite a lot of fMRI research was performed in this domain, the neurofunctional basis of the disturbances is still only incompletely known. Most studies used simple repetitive motor activities (e.g., sequential finger opposition) alternating with resting conditions in a block-design approach. Early investigations [e.g., the work of Wenz (1994) or Schröder and colleagues (1995)] reported hypoactivation of primary sensorimotor and supplementary motor cortices in schizophrenia, a finding not consistently replicated by subsequent studies (Braus *et al.*, 1999; Buckley *et al.*, 1997; Schröder *et al.*, 1995, 1999; Wenz *et al.*, 1994). In addition, data indicating altered functional asymmetry of the cortical hemispheres during motor tasks have been published [e.g., recently by the group of Yurgelun-Todd (2004); Bertolino *et al.*, 2004a; Mattay *et al.*, 1997; Rogowska *et al.*, 2004].

One emerging finding is that patients with schizophrenia may be characterized by a reduced lateralization index during motor performance. In light of the usually pronounced lateralization of cortical activation during motor function, this indicates an abnormal situation in terms of reduced contralateral recruitment or deficient ipsilateral inhibition of motor areas, respectively. However, a substantial number of contradictory findings, as well as some empirical data (Bertolino *et al.*, 2004a; Braus *et al.*, 1999; 2000b), show that further studies in

these areas will benefit from controlling for confounding factors such as medication effects (see also pharmacological section of this review).

II. Early Visual Processing Deficits

Neuropsychological research has repeatedly confirmed the presence of visual information-processing deficits in schizophrenia (Braff and Saccuzzo, 1981, 1985; Keri *et al.*, 2000; Moritz *et al.*, 2001). Among others, patients exhibit a significantly increased error rate during performance of so-called backward masking tasks, which use contiguous distractor presentations to disturb the sensory processing of target stimuli (Braff and Saccuzzo, 1981, 1985). Another affected visual domain is deficient perceptual discrimination of target velocities, a research area extensively investigated by Holzman and coworkers (Chen *et al.*, 1999a,b,c). Because some studies indicate that visual-processing abnormalities may be observable in asymptomatic relatives of patients with schizophrenia (Chen *et al.*, 1999b; Green *et al.*, 1997), they may be valuable as a trait marker of disease vulnerability. Delineation of the underlying neural-processing deficit may, therefore, be valuable as an endophenotype.

Consequently, much research has been directed at the characterization of visual information-processing deficits in behavioral experiments. Here, high error rates during processing of stimuli of higher spatial frequency, or moving stimuli, suggest a pathophysiological involvement of the dorsal visual-processing stream in patients with schizophrenia (Cadenhead *et al.*, 1998; O'Donnell *et al.*, 1996; Schwartz *et al.*, 1999). The so-called magnocellular network comprises cortical areas specialized for the handling of motion and depth cues (e.g., the motion-sensitive field V5 [hMT], posterior-parietal cortex [PPC], and frontal eye fields [FEF]; Ungerleider and Mishkin, 1982; Ungerleider *et al.*, 1998). The exact location of the presumed dorsal stream dysfunction, however, cannot be identified by use of a behavioral approach. Prior empirical data were, therefore, interpreted in manifold ways [e.g., as a sign of a deficient prefrontal control of lower visual areas or a thalamic filter dysfunction (Keri *et al.*, 2000; Levin, 1984a,b)]. Among others (Chen *et al.*, 1999a; Stuve *et al.*, 1997; Tek *et al.*, 2002), the group surrounding Holzman (Chen *et al.*, 1999a,b,c) assumes a "bottom-up" processing of motion signals in V5 as being responsible for visual processing dysfunctions and executive deficits observable in patients with schizophrenia (e.g., eye-tracking dysfunction, spatial working memory deficits).

Only relatively few research groups have used fMRI to study early visual-information processing in schizophrenia to date. One of our own studies (Braus *et al.*, 2002) investigated visuoacoustic integration in 12 neuroleptic-naive patients with a passive stimulation paradigm involving the simultaneous presentation of a

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used fMRI to study early visual- ate. One of our own studies (Braus ion in 12 neuroleptic-naive patients the simultaneous presentation of a visual 6-Hz checkerboard and an auditory drumbeat stimulus. Compared with healthy controls, the patient group displayed a significant activation decrease in both the thalamic geniculate body and higher order areas of the dorsal processing stream (PPC, FEF, and DLPFC). The results indicate a fundamental visual-processing deficit of the dorsal stream network that is already noticeable at disease onset, even in the absence of marked cognitive demands (Braus *et al.*, 2002). Subsequent fMRI studies of our group examined the pathophysiological model supposed by Holzman and colleagues, proposing a circumscribed functional deficiency of V5 during visual motion perception. In a first step, we examined brain functional correlates of patients with schizophrenia and healthy controls during the passive perception of moving visual targets (Tost *et al.*, 2003a). The stimulation paradigm consisted of a pseudo-randomized presentation of tilted and moving sinusoidal gratings, permitting the identification of V5 in the occipitotemporal association cortex (see Fig. 1). Data analysis confirmed a strong recruitment of the dorsal processing network in both groups. Furthermore, group comparison verified a significantly enhanced activation of controls in posterior-parietal areas, whereas activation differences in V5 were absent (see Fig. 2).

The assumption of deficient processing of motion signals in V5 is largely based on behavioral experiments indicating a significantly lower contrast sensitivity for the discrimination of small-velocity differences in schizophrenia (Chen *et al.*, 1999c). Thus, in a second step, we examined the neurobiological background of this phenomenon with fMRI (Tost *et al.*, 2003b, 2004). The block design fMRI paradigm included the sequential presentation of moving sinusoidal gratings with varying velocity differences, presented in a pseudo-randomized manner (easy task condition: 11°/s vs. 5°/s; difficult task condition: 8°/s vs. 6°/s). Patients with schizophrenia and healthy controls were instructed to indicate the faster grating of each stimulus pair during the scan. In both groups, task performance yielded a significant activation enhancement of a highly distributed visuomotor network, including subcortical parts of the visual system (lateral geniculate nucleus), primary and extrastriate visual cortices (V1–V5), and higher order areas of the dorsal visual processing stream (PPC, SMA, lateral premotor cortex, DLPFC, see Fig. 3). Direct comparison of the easy and difficult target discrimination revealed a load-dependent activity enhancement in posterior-parietal and prefrontal cortices but not V5. Interaction analysis disclosed a significantly decreased activation of PPC and DLPFC in the patient group; activation differences in V5, however, could not be verified. In summary, our own functional imaging results do not support a popular hypothesis deduced from behavioral data, suggesting a circumscribed processing deficit of the visual motion area V5 in schizophrenia. Instead, our results point to a deficient processing of motion cues at a higher level of the dorsal visual network usually associated with executive functioning, the control of eye movements,

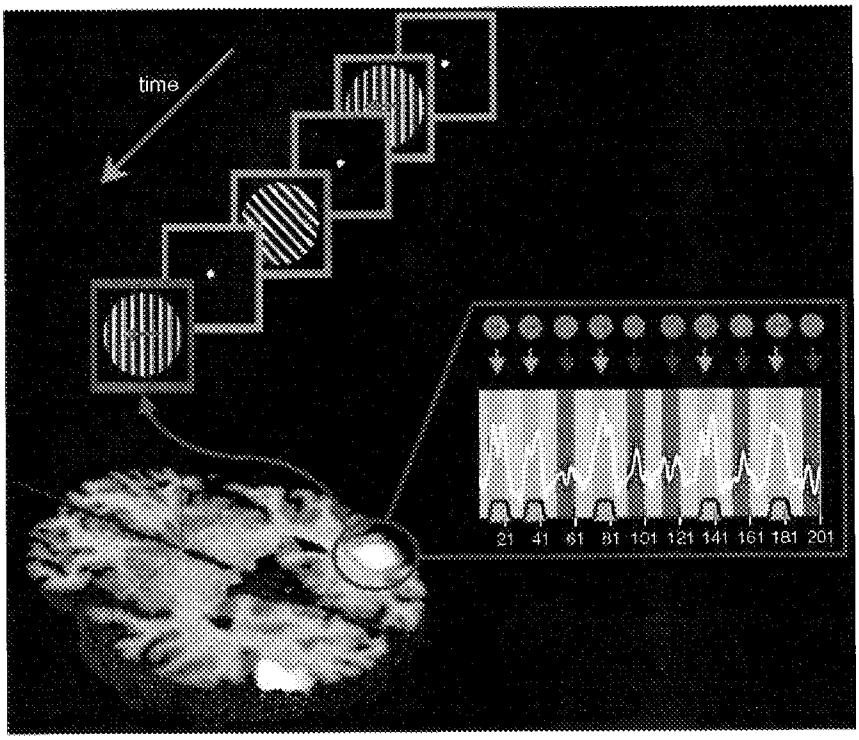
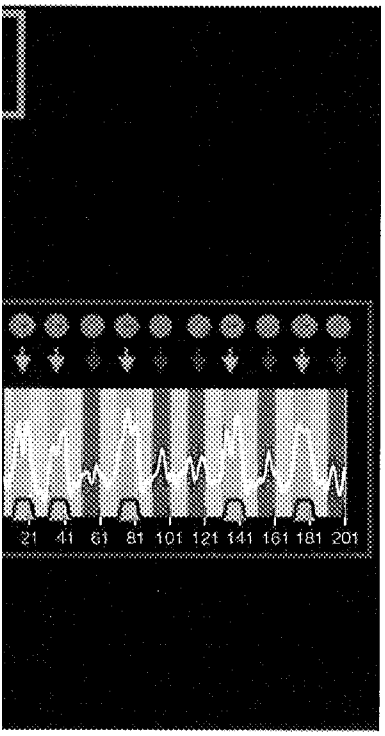


FIG. 1. Visual motion perception paradigm. Statistical comparison of the different stimulation conditions in a general linear model analysis (moving vs. stationary gratings) allows the identification of the motion-sensitive processing area V5 (hMT) in the occipital temporal association cortex. (See Color Insert.)

and the "top-down" control of lower visual cortices (Kastner *et al.*, 1998, 1999; Ungerleider *et al.*, 1998).

III. Auditory System

The perception of voices in the absence of external stimuli (auditory hallucinations) is one of the cardinal symptoms of schizophrenia. Cognitive models first suggested underlying abnormalities in the processing of inner speech, a notion not supported by functional imaging studies. Instead, in the past 15 years, empirical evidence repeatedly indicated structural and functional disturbances of the superior temporal gyrus (STG), a crucial part of the network controlling the perception and production of speech. A close relationship between the



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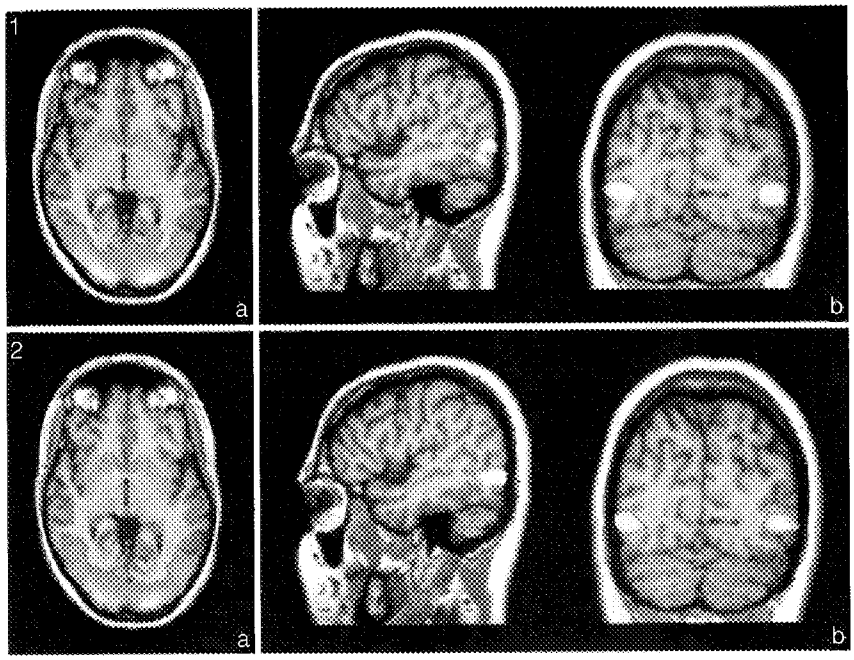


FIG. 2. Comparison of striate and extrastriate visual processing areas V1 V5 (contrast a: stationary + moving visual stimuli > baseline) and the motion-selective processing area V5 (contrast b: moving stimuli > stationary stimuli) in healthy controls (1) and schizophrenic patients (2). No significant group differences are evident in the lower parts of the dorsal visual network (interaction analysis $p \leq 0.0001$, uncorrected). (See Color Insert.)

severity of auditory hallucinations and the extent of STG volume reduction, for instance, was already found by Bartha and colleagues in 1990 (Barta *et al.*, 1990). Functional imaging results provided by the groups of Schnorr (1995), Murray (1993, 1995), and Woodruff (1995, 1997) demonstrated a pronounced activity enhancement of auditory- and speech-processing cortices during hallucinatory experiences (Heschl's gyrus, Broca and Wernicke area) (McGuire *et al.*, 1993, 1995; Silbersweig *et al.*, 1995; Woodruff *et al.*, 1995, 1997). A particularly convincing study was conducted by Dierks *et al.* (1999), which demonstrated the potential of event-related fMRI study designs for psychiatric research. From a neuroscientific point of view, these results yield a plausible explanation for the fact that patients accept the internally generated voices as real.

Consistent with the proposal of a regional disconnection syndrome contributing to the symptomatology of schizophrenia, current fMRI, DTI, and morphometric imaging data indicate a correlation of hallucination severity with the extent of the functional and structural connectivity abnormalities of the STG

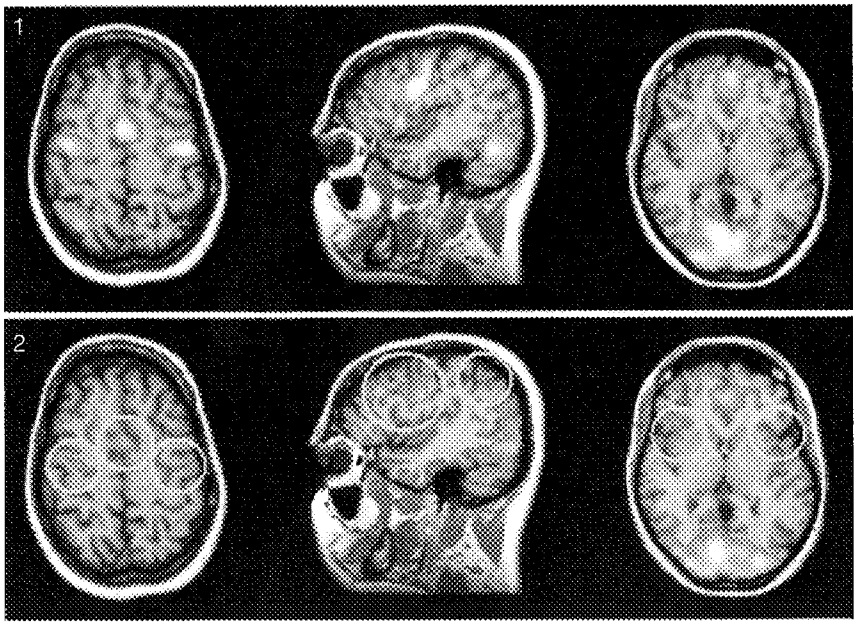
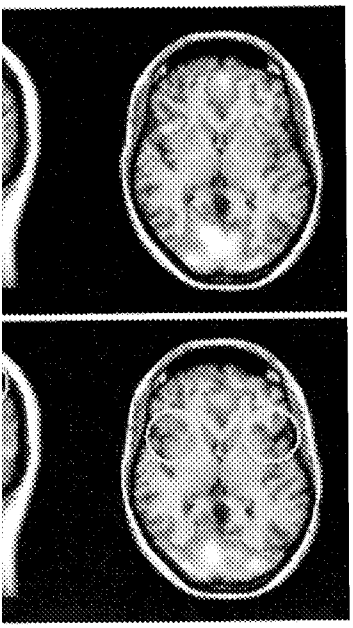


FIG. 3. Visuomotor activation associated with the discrimination of target velocities. Compared with the healthy controls (1), schizophrenic patients (2) display a significant activation decrease in higher order areas of the dorsal visual processing stream (premotor cortex, SMA, PPC, insular cortex, ACG; interaction analysis $p \leq 0.0001$, uncorrected). (See Color Insert.)

(Gaser *et al.*, 2004; Hubl *et al.*, 2004; Lawrie *et al.*, 2002). Furthermore, these alterations have been shown to interfere with the cortical processing of regular auditory stimuli in schizophrenia as well. An fMRI study of Wible and coworkers (2001), for example, provided evidence for a dysfunctional processing of mismatch stimuli (a descriptive term for the presentation of differing tones embedded in a series of standard tones) in the primary auditory cortex (Wible *et al.*, 2001). Other fMRI studies point to a diminished response of the temporal lobes to external speech during hallucinatory experiences (David *et al.*, 1996; Woodruff *et al.*, 1997). This phenomenon is usually explained as the competition of physiological and pathological processes for limited neural processing capacity.

IV. Selective Attention

The neuropsychological term attention describes the selection and integration of relevant information units from the perceptual stream, requiring the complex interplay of different brain regions and functions. In schizophrenia



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research, scientific descriptions of attentional dysfunction can be traced back to the initial descriptions by Kraepelin and Bleuler. These disturbances are considered by some as promising cognitive endophenotypes of disease vulnerability, because they precede disease onset, persist during remissions, and are also found in asymptomatic relatives (Cornblatt and Malhotra, 2001; Egan *et al.*, 2000; Gold and Thaker, 2002).

The continuous performance test (CPT)—rather a terminological label than a standardized test device—is one of the most popular neuropsychological measures in schizophrenia research. The term encompasses a variety of tasks best summarized as requiring selective attention (typical task requirements: selective responses to certain targets, inhibition of inadequate reactions to non-targets, high rate of stimuli over a period of less than 10 minutes). Apart from simple choice reaction tasks (involving the selection of a certain target from an assortment of stimuli, CPT-X) more complex CPT versions with additional cognitive requirements can be distinguished. So-called degraded CPTs use blurred visual presentations to manipulate the perceptual requirements of the task (e.g., Siegel *et al.*, 1995). Appropriate handling of contingent CPTs requires the additional monitoring of preceding task conditions. Because of their strong resemblance to 1-back tasks, these cognitive tests extend into the working memory domain (e.g,. CPT-AX, CPT-IP, and CPT-double-T). Other CPT variants use interspersed distractors to assay impulse control; the resulting task demands are similar to classic cognitive interference tasks (e.g., Stroop). Thus, any assessment of functional imaging findings in this domain needs to carefully take the specific task arrangements into account.

So far, most functional imaging studies have used contingent CPTs to examine selective attention dysfunction in schizophrenia. Dorsolateral prefrontal hypoactivation of the patient group is a widely replicated finding, likely because of the moderate working memory load of the tasks (MacDonald and Carter, 2003; Volz *et al.*, 1999). Barch and coworkers (2001) observed a comparable DLPFC dysfunction in neuroleptic-naive patients as well, arguing against medication effects (Barch *et al.*, 2001). Simple CPT choice-reaction tasks, however, were rarely investigated with fMRI. Only one study by Eyler and colleagues (2004) used a simple CPT paradigm, providing evidence for a right inferior frontal activation decrease in the patient group. The authors hypothesized that the unusual ventral lateral location of the group difference may be a consequence of the lower executive demands of their task (Eyler *et al.*, 2004).

An important neural interface of cognition, emotion, and behavioral control, the dorsal anterior cingulate gyrus (ACG) is prominently activated during the performance of cognitive interference tasks (Cohen *et al.*, 2000). Early PET studies already showed ACG hypoperfusion during interference in schizophrenia (Carter *et al.*, 1997). According to Yücel and colleagues (2002), the activation loss may coincide with the absence of a morphologically differentiated paracingulate

gyrus in patients (Yücel *et al.*, 2002). Several studies conducted by Carter, Barch, Cohen, and colleagues demonstrated a comparatively specific (performance correlated) ACG dysfunction in schizophrenia (Carter *et al.*, 1999, 2001); the authors extended their results into a framework encompassing computational models of prefrontal dopamine function (Braver *et al.*, 1999). An fMRI study conducted by Heckers and coworkers (2004) confirmed, even under comparable task performance conditions, an absence or abnormal localization of dorsal ACG activation in patients with schizophrenia (Heckers *et al.*, 2004). The described functional ACG results are supplemented by growing DTI evidence indicating disturbed integrity of the cingulate bundle (Kubicki *et al.*, 2003; Sun *et al.*, 2003). Although the total number of studies on this topic is still limited to date, current evidence for a structural and functional disturbance of the anterior cingulate gyrus in schizophrenia is convincing (Weiss *et al.*, 2003).

V. Working Memory Dysfunction

The institution and flexible adaptation of behavioral patterns depending on environmental demands is one of the main functions of prefrontal cortex. The high rate of so-called executive dysfunction (e.g., working memory abnormalities) thus argues for involvement of the prefrontal regions in the pathogenesis of schizophrenia (Glahn *et al.*, 2000; Gold *et al.*, 1997; Goldman-Rakic, 1994; Silver *et al.*, 2003). Unlike short-term memory, the working memory concept is aimed at the active storage of information necessary for the performance of cognitive operations but not available from the environment. So-called "n-back" tasks are a popular neuropsychological instrument for the assessment of working memory dysfunction. Here, participants are required to constantly monitor a sequence of stimulus presentations and react to items that match the one presented "n" stimuli previously. These tasks are popular, because working memory load can be increased parametrically by increasing the parameter "n" (1-back, 2-back, etc.) while keeping stimulus and response conditions constant. Another popular measure of executive function is the Wisconsin card sorting test (WCST), a complex task requiring abstract reasoning and cognitive flexibility in addition to working memory.

Both instruments have been used extensively in imaging research to examine the neurobiological correlates of frontal lobe dysfunction in schizophrenia. Patients with schizophrenia display irregular activation patterns during working memory tasks regardless of performance level (Honey *et al.*, 2002), motivation (Berman *et al.*, 1988), or the particular stimulus material used (Spindler *et al.*, 1997; Stevens *et al.*, 1998; Tek *et al.*, 2002; Thermenos *et al.*, 2004). Comparable differences can also be observed in healthy siblings of patients with schizophrenia

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(Callicott *et al.*, 2004). The precise mechanism of the prefrontal functional deficit, however, is still a matter of some debate. Most early functional imaging studies indicated a DLPFC hypoactivation, both at rest and during working memory performance (Andreasen *et al.*, 1997; Paulman *et al.*, 1990; Volz *et al.*, 1999). Discrepant results, however, accumulated in the past several years have made it necessary that the theory of a pure "hypofrontality" in schizophrenia had to be revised, or at least amended (Manoach *et al.*, 1999, 2000; Ramsey *et al.*, 2002).

Several lines of evidence support the contention that the simple descriptive term of a hypoactivation or hyperactivation underestimates the real complexity of the issue (Callicott *et al.*, 2003). Even in healthy subjects, for instance, DLPFC activation follows a complex and load-dependent course similar to an inverted U function. According to this, prefrontal activation level increases with task demands until a capacity limit is reached, followed by DLPFC activation decrease concomitant with behavioral decompensation (as indicated by the corresponding increase of performance errors) (Callicott *et al.*, 1999). A comparable relationship between working memory effort and amount of prefrontal neural discharge was observed in animal studies (Goldman-Rakic *et al.*, 2000). Second, some groups have observed an increase of activation as subjects exceed their capacity limit (Mattay *et al.*, 2003), arguing for an "(in)efficiency" concept in which increased activation may be indicative of excessive and task-inadequate neuronal recruitment. A further complication is derived from the fact that neuroimaging data typically reflect a mapping of statistical significance levels representing composite measures of "signal" and "noise" (as measured by the mean shift in BOLD effect and the residual variance, respectively) that may correspond to differing neuronal phenomena in the context of working memory. Recent reviews have attempted to reconcile discrepant findings in this domain in the context of more complex functional models (Callicott *et al.*, 2000; Manoach, 2003).

Current pathophysiological theories, therefore, assume deficient neural processing in patients with schizophrenia that may, depending on the current capacity reserve, manifest as prefrontal hyperactivation or hypoactivation, respectively. The course of the DLPFC activation level may thus correspond to a pathological left shift in the inverted U load-response curve described previously: patients may display a relatively enhanced prefrontal activation level under low cognitive load (hyperactivity subsequent to the inefficient use of neural resources), whereas the reverse may be found under increasing working memory demands (hypoactivity as sign of neural capacity constraints) (Jansma *et al.*, 2004; Manoach *et al.*, 2000). A recent article by Callicott and colleagues (2003) found group differences in DLPFC activation, supporting the pathophysiological model of a shifted inverted U function in schizophrenia (Callicott *et al.*, 2003). However, findings not compatible with this model were noted, as well. The functional correlates of DLPFC dysfunction thus seem to manifest as a highly complex,

capacity-dependent pattern of coincident hyperactivity and hypoactivity states. The main commonality of most studies seems to be less the directionality than the location of the abnormality, namely, the middle frontal gyrus and the corresponding Brodmann areas 46 and 9. More work will be necessary before a theoretical account can be reached that encompasses the current empirical data while remaining predictive enough to be potentially falsifiable.

VI. Antipsychotic Drug Effects

The psychopharmacology of schizophrenia has progressed in the past 10 years, focusing on the development of novel antipsychotic drugs with an atypical effect profile (e.g., clozapine, amisulpride, olanzapine). Some studies indicate that, compared with typical neuroleptic drugs (e.g., haloperidol), these substances may be superior with regard to the treatment of negative symptoms and cognitive deficits (Meltzer and McGurk, 1999; Meltzer *et al.*, 1994). Although other studies have shown no such advantage, the absence of substantial extrapyramidal side effects is a definite improvement in patient quality of life in many cases. Until the mid-nineties, research on antipsychotic drug effects was mainly limited to behavioral experiments (Lieberman *et al.*, 1994; Nestor *et al.*, 1991; Zahn *et al.*, 1994). MRI studies examining structural, functional, and metabolic correlates of antipsychotic drug treatment emerged at the turn of the last century (Arango *et al.*, 2003; Bertolino *et al.*, 2001; Braus *et al.*, 2001; Ende, 2000; Ende *et al.*, 2000; Heitmiller *et al.*, 2004).

To date, most functional MRI studies in this field have been aimed at drug-induced changes of voluntary motor control and executive functioning. In this context, favorable effects of atypical antipsychotics on putative functional disturbances in schizophrenia have been repeatedly reported (Ramsey *et al.*, 2002). A recent study by Bertolino and coworkers (2004), for instance, shows a normalization of sensorimotor hypoactivation in the course of olanzapine treatment (Bertolino *et al.*, 2004a). Another longitudinal study conducted by the group of Andreasen (2001) showed normalized functional connectivity of cortico-talamic-cerebellar-cortical circuits with the same agent (Stephan *et al.*, 2001). Furthermore, several older studies suggest at least partially beneficial treatment effects. Especially prefrontal functions showed some degree of normalization with atypical (but not typical) antipsychotic drug treatment (Braus *et al.*, 1999; 2000a,b,c; Honey *et al.*, 1999). This notion is supported by MR spectroscopy data indicating a higher level of the neuronal viability marker *N*-acetylaspartate (NAA) in patients receiving atypical treatment (Bertolino *et al.*, 2001) as opposed to patients with typical antipsychotics (Ende *et al.*, 2000).

A conclusive picture does not currently emerge from imaging results on antipsychotic drug effects conducted to date. The amount of scientific publications on this topic is still small, and methodologically necessary study designs (e.g., double-blind) are almost completely lacking. Given the cross-sectional design of most of the studies, the conclusion of a "normalizing" or "restoring" drug effect—drawn by some authors from reductions or absence of fMRI group differences—must remain tentative. Furthermore, even in longitudinal study designs, a demonstration of functional recovery is conditional on the reliable and valid characterization of the underlying pathology. As reviewed, however, for most of the studied domains, the functional correlate of the schizophrenic deficit syndrome is not yet precisely delineated. This may account for some drug effect inconsistencies reported (e.g., compare the data provided by Ramsey *et al.* and Honey *et al.* in Table I: drug-induced restoration of executive functions may manifest as enhanced activation subsequent to a pathological hypoactivity or reduced activation after a pathological hyperactivity). Future fMRI studies with more complex study designs will certainly be capable of dissolving this apparent heterogeneity (e.g., double-blind investigation of genetically defined responder groups). Convergent observations indicating an association of functional and clinical improvement with the COMT genotype are major steps in this direction (Bertolino *et al.*, 2004b).

VII. Neuroimaging Genomics

The completion of the draft sequence of the human genome was a pivotal achievement that profoundly changed all aspects of medicine and is beginning to transform neuroimaging in psychiatry as well. The characterization of the effects of genomic variation on neural systems level function using neuroimaging promises to yield decisive insights into both normal and dysfunctional processes important for protective and risk factors for mental illness (Gould and Husseini, 2004). In the case of schizophrenia, it seems overwhelmingly likely that the substantial genetic component of the disease risk is conferred by multiple, interacting, individually small-risk or susceptibility genes. A promising strategy is, therefore, the characterization of convergent pathways involved in the effects of genomic variation in such risk genes (e.g., dysbindin, neuroregulin 1, catechol-O-methyltransferase COMT, BDNF) on neural function. This work will usually commence after gene identification by linkage, association, or candidacy (Harrison and Weinberger, 2004). Even further in the future may be the opposite strategy, whereby systems-level endophenotypes, such as those defined by neuroimaging, may become useful in gene-finding efforts.

TABLE I

RECENT fMRI FINDINGS IN SCHIZOPHRENIA RESEARCH

	Author (year)	Study results
Voluntary motor control	Rogowska *et al.* (2004)	Reduced activation of sensorimotor cortices and altered hemispherical asymmetry during sequential finger opposition (SFO) (Rogowska *et al.*, 2004).
	Menon *et al.* (2001)	Reduced activation level and disturbed functional connectivity of the thalamus and lentiform nucleus (Menon *et al.*, 2001).
	Schröder *et al.* (1999)	Hypoactivation of sensorimotor cortices and highly variable task performance during pronation-supination (Schröder *et al.*, 1999).
Visual system	Tost *et al.* (2004)	Significant activation decrease of PPC and DLPFC during the discrimination of different target velocities (Tost *et al.*, 2004).
	Tost *et al.* (2003)	Passive motion perception: significant hypoactivity of PPC, no significant group differences in the motion-sensitive visual area V5 (Tost *et al.*, 2003a).
	Braus *et al.* (2002)	Neuroleptic-naive patients: hypoactivity of the thalamus and higher areas of the dorsal processing network under visuoacoustic stimulation (Braus *et al.*, 2002).
Auditory system	Laurie *et al.* (2002)	Frontotemporal connectivity decrease is correlated with severity of auditory hallucinations (Lawrie *et al.*, 2002).
	Wible *et al.* (2001)	Reduced STG activation during auditory mismatch points to an early central processing deficit in the auditory system (Wible *et al.*, 2001).
	Dierks *et al.* (1999)	Hallucination experiences are associated with an activation enhancement of the primary auditory cortex (Dierks *et al.*, 1999).
	Woodruff *et al.* (1997)	Limited response of speech processing areas to external stimulation during auditory hallucinations (Woodruff *et al.*, 1997).
Selective attention	Eyler *et al.* (2004)	Simple choice reaction: significant activation decrease of the right inferior-frontal cortex despite comparable task performance (CPT-X) (Eyler *et al.*, 2004)
	Heckers *et al.* (2004)	Cognitive interference: dislocated or absent activation of the dorsal ACG, same task performance rate and accuracy (Heckers *et al.*, 2004).
	Weiss *et al.* (2003)	Cognitive interference: additional recruitment of DLPFC and ACG resources, comparable task accuracy (Weiss *et al.*, 2003).

		processing network under visuoacoustic stimulation (Braus *et al.*, 2002).
Auditory system	Laurie *et al.* (2002)	Frontotemporal connectivity decrease is correlated with severity of auditory hallucinations (Lawrie *et al.*, 2002).
	Wible *et al.* (2001)	Reduced STG activation during auditory mismatch points to an early central processing deficit in the auditory system (Wible *et al.*, 2001).
	Dierks *et al.* (1999)	Hallucination experiences are associated with an activation enhancement of the primary auditory cortex (Dierks *et al.*, 1999).
	Woodruff *et al.* (1997)	Limited response of speech processing areas to external stimulation during auditory hallucinations (Woodruff *et al.*, 1997).
Selective attention	Eyler *et al.* (2004)	Simple choice reaction: significant activation decrease of the right inferior-frontal cortex despite comparable task performance (CPT-X) (Eyler *et al.*, 2004)
	Heckers *et al.* (2004)	Cognitive interference: dislocated or absent activation of the dorsal ACG, same task performance rate and accuracy (Heckers *et al.*, 2004).
	Weiss *et al.* (2003)	Cognitive interference: additional recruitment of DLPFC and ACG resources, comparable task accuracy (Weiss *et al.*, 2003).
Working memory	Barch *et al.* (2001)	New York1-back: deficient DLPFC activation in neuroleptic-naive patients; unobtrusive inferior frontal activation pattern (CPT-AX) (Barch *et al.*, 2001).
	Volz *et al.* (1999)	1-back: significant hypoactivation of mesial frontal and cingulate areas during CPT performance (CPT-TT) (Volz *et al.*, 1999).
	Callicott *et al.* (2004)	Significantly enhanced recruitment of prefrontal resources in healthy siblings (n-back) (Callicott *et al.*, 2004).
	Schlosser *et al.* (2003)	Altered effective connectivity of cerebellum-thalamus (↓), cerebellum-frontal lobe (↓), and thalamus-cortex (↑) (n-back) (Schlosser *et al.*, 2003).
	Callicott *et al.* (2003)	Deficient neural processing strategy: advanced hypofrontality with higher working memory demands, preservation of task performance leads to a functional overload of DLPFC resources (n-back) (Callicott *et al.*, 2003).
	Manoach *et al.* (2000)	Patients show a left prefrontal hyperactivity and enhanced spatial heterogeneity of prefrontal activation patterns (Manoach *et al.*, 2000).
	Callicott *et al.* (1999)	Load-dependent course of the BOLD response in healthy subjects: inverted U-shaped function with increasing task demands (n-back) (Callicott *et al.*, 1999).
	Callicott *et al.* (1998)	DLPFC hypoactivation in the patient group, not attributable to motion artifacts (n-back) (Callicott *et al.*, 1998).
	Volz *et al.* (1997)	Decreased activation of the right prefrontal cortex (WCST) (Volz *et al.*, 1997).
Medication effects	Bertolino *et al.* (2004)	Motor control (L*): improvement of sensorimotor hypoactivation with olanzapine, unchanged lateralization disturbance (Bertolino *et al.*, 2004a).
	Ramsey *et al.* (2002)	Abstract reasoning (X*): neuroleptic-naive patients excessively recruit frontal areas, regular activation level in atypically medicated patients (Ramsey *et al.*, 2002).
	Stephan *et al.* (2001)	Motor control (L*): normalization of cerebellar functional connectivity after olanzapine administration (Stephan *et al.*, 2001).
	Braus et al. (2000)	Visual information processing (X*): selective prefrontal BOLD-attenuation in typically (but not atypically) medicated patients (Braus et al., 2000b).
	Braus *et al.* (1999, 2000)	Motor control (X*): selective sensorimotor BOLD-attenuation in patients under typical neuroleptics. Regular activation patterns in neuroleptic-naive first episode- and atypically medicated patients, respectively (Braus *et al.*, 2000b; Braus *et al.*, 1999).
	Honey *et al.* (1999)	Working memory (L*): medication switch from typical neuroleptics to risperidone induces an activation enhancement of PPC and DLPFC (Honey *et al.*, 1999).

(*Continued*)

TABLE I (*Continued*)

	Author (year)	Study results
Molecular brain imaging	Egan *et al.* (2004)	GRM3 metabotropic glutamate receptor variation is associated with an enhanced risk for schizophrenia, inefficient activation of DLPFC (working memory), hippocampal activation decrease (episodic memory), attenuated prefrontal NAA-levels, and executive cognitive deficits (Egan *et al.*, 2004).
	Egan *et al.* (2001)	Dopamine catabolism: COMT val-allele is associated with an enhanced risk for schizophrenia, inefficient activation of DLPFC (working memory), and executive cognitive deficits (Egan *et al.*, 2001).

*X, cross-sectional design; L, longitudinal design.

Egan *et al.* (2001)	X	L	Dopamine catabolism: COMT val-allele is associated with an enhanced risk for schizophrenia, inefficient activation of DLPFC (working memory), and executive cognitive deficits (Egan *et al.*, 2001).

*X, cross-sectional design; L, longitudinal design.

Current work has largely focused on functional polymorphisms with at least partially characterized effects on their gene products. A common Val108/158Met substitution in the gene for COMT, for example, leads to a substantial decrease in the activity of this major enzyme in dopamine catabolism (Chen *et al.*, 2004). Another well-studied example outside the domain of schizophrenia is the 5-HTTPLR polymorphism in the promoter region of the serotonin transporter (Hariri *et al.*, 2002). Hariri and Weinberger (2003) enumerate requirements for experimental design in neuroimaging genomics (Hariri and Weinberger, 2003): use of well-characterized behavioral probes; control of confounding variables such as age, performance, IQ; and control of genomic confounds. The often-small effects referable to genetic variation in susceptibility genes require large sample sizes and convergent evidence from multimodal imaging (structural, functional, neurochemical) combined with cognitive and clinical data (Egan *et al.*, 2004). As in the field of psychiatric genetics as a whole, the definition and validation of useful statistical standards guiding work in this area is still in flux.

The first example of this approach in schizophrenia was the characterization of the effect of the COMT polymorphism on cognition, prefrontal function, and risk for schizophrenia by Egan and coworkers (Egan *et al.*, 2001). This finding was subsequently independently replicated (Bilder *et al.*, 2004; Goldberg *et al.*, 2003) and extended to other psychiatric conditions as well (Tiihonen *et al.*, 1999; Zubieta *et al.*, 2003). A similar multimodal approach was recently used by the same group to characterize a risk haplotype in a gene encoding a metabotropic glutamate receptor (GRM3), demonstrating inefficient prefrontal response, reduced neuronal integrity in prefrontal cortex, hypoactivation of the hippocampus during episodic memory, as well as impaired cognitive performance during verbal memory associated with an identified genetic variation conferring increased risk for schizophrenia. This work represents a major advance, because the risk haplotype as such did not have a direct functional correlate on the genetic/molecular level because it was composed of noncoding single nucleotide polymorphisms. Rather, the imaging work itself provided crucial convergent evidence that this risk haplotype has functional effects (Egan *et al.*, 2004).

The characterization of susceptibility gene mechanisms using multimodal neuroimaging is likely to increase in importance in the coming years and substantially enrich our understanding of the pathophysiology of schizophrenia. The first studies in this emerging field attest to the unexpectedly high power of imaging approaches to delineate genomic variation. It is to be hoped that the detection of convergent functional pathways of diverse risk genes will lead not only to better understanding of the illness but also to the discovery of novel treatment targets. In any case, functional neuroimaging will likely retain its pivotal role in the characterization of systems-level mechanisms linking the genetic-molecular level to mental and social phenomena.

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